

Early Versus Late Dialysis



By
Tarek M El Tantawy

Consultant Nephrology
DM, MSc Nephrology ASU
HQM- Cambridge

Disclosure

- ✓ Chronic kidney disease.
- ✓ Initiation of dialysis.
- ✓ Goals of dialysis.
- ✓ When to start dialysis: Early versus Late.
- ✓ Who (has) said early dialysis is good.
- ✓ Who (has) said early dialysis is bad.
- ✓ Nephrological referral.
- ✓ IDEAL study.
- ✓ Conclusions.



Chronic Kidney Disease



Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			



Chronic kidney disease (CGA stages)



	Examples of systemic diseases affecting the kidney	Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative GN; focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary-tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies



Initiation of dialysis

- ✓ The decision to initiate dialysis in a patient with ESRD involves the consideration of **subjective** and **objective** parameters by the physician and the patients.
- ✓ The decision to start maintenance dialysis should not be solely based upon serum creatinine or estimated GFR.
- ✓ It has a negative psychological impact on patients “ **BAD NEWS**”.
With Important socio-economic implication.
- ✓ Patient education is a central tenet of optimal initiation of dialysis.
- When to start dialysis is a subject to be controversy.

From the current DaVita website USA)...

The patient information sites

✓ If I have kidney disease, will I need dialysis?

(In the early stages of chronic kidney disease, you do not need dialysis. The stages of chronic kidney disease can last for many years. But if your kidneys fail, you will need dialysis or a kidney transplant to keep you alive).

✓ When should I start dialysis?

“National Kidney Foundation guidelines recommend you start dialysis when kidney function drops to 15% or less”...

(... or if you have severe symptoms caused by your kidney disease, such as: shortness of breath, fatigue, muscle cramps, nausea or vomiting).

- ✓ One could well ask why these patients are still being given this early start information?
- ✓ One could be **cynical** and conclude that the dialysis-for-profit might 'encourage' an early start.

Or

- ✓ *Be more **benevolent** and conclude that some may just be unaware of the data.*

Goals of dialysis



- ✓ Free of uremic symptoms.
 - ✓ Control volume overload, acid - base and electrolyte disorders.
 - ✓ Provide clearance of uremic toxins enough to allow an adequate dietary protein and caloric intake.
-
- *When residual kidney functions fail to maintain all these vital functions, we have a solid argument for starting dialysis therapy.*
 - *Since an important goal of dialysis is to enhance quality of life as well as to prolong survival.*

When to start dialysis: Early versus Late

- ✓ The key question is whether we have to start dialysis prior to, or after the overt development of these uremic symptoms and signs.
- ✓ The beneficial effects that dialysis can offer to the pre-dialysis renal failure patients.
- ✓ *The potential complications of dialysis, and the changes in the way of life that many patients have to endure, are factors which should temper this decision.*

KDIGO: Initiation of dialysis



5.3: TIMING THE INITIATION OF RRT:

5.3.1: Dialysis is to be initiated when one or more of the following are present:

- ✓ Symptoms or signs attributable to kidney failure: (serositis, acid-base or electrolyte abnormalities, Pruritus).
- ✓ Inability to control volume status or blood pressure.
- ✓ A progressive deterioration in nutritional status refractory to dietary intervention.
- ✓ Cognitive impairment.

This often but not invariably occurs in the GFR range between 5 and 10 ml/min. (2B)

Who (has) said early dialysis is good

Bonomini et al, 1985

- ☆ Reported that an early start of dialysis was associated with reduced mortality and morbidity.
- ✓ Among a subset of patients who were subsequently transplanted, there was **a survival advantage** for those started dialysis **early** (n = 50) vs **later** (n= 96), as well as **less vascular calcification, bacterial infection, dyslipidemia and hospitalization**.

Who (has) said early dialysis is good

Tatterssal et al (Am J Nephrol 15: 283- 2 89, 1995)

- ✓ Prospective cohort study of 63 patients in 1991-92.
- ☆ Demonstrated **reduced survival** in patients with less residual renal functions at start of dialysis , although these patients were also significantly older and had significantly more co-morbidity.
- ✓ **Hospitalization length of stay was greater** among those with residual $Kt/V < 1.5$ ml/minute at the time of initiation of dialysis.

Who (has) said early dialysis is good

Schulman G and Hakim RM:

Improving outcomes in chronic hemodialysis patients: should dialysis be initiated earlier? Semin Dial 1996; 9(3): 255-9

- ✓ Patients initiated on dialysis with a creatinine clearance >10 ml/minute had an 88% 10-years **survival** when compared to 55% in those initiated a creatinine clearance of less than < 10 ml/minute (mean 4 ml/ minute).

Who (has) said early dialysis is good

NKF (1997):

- ✓ Start dialysis with **eGFR ~10.5** ... on the basis of the minimum target level of total clearance (residual renal and dialysis) for peritoneal dialysis.

KDOQI (2006):

- ✓ RRT should be considered at
 - **eGFR < 15****OR**
 - **eGFR > 15**when patients have 'co-morbidities' or symptoms of uremia.



FDA approves Victor Gura MD

Who (has) said early dialysis is bad

Beddhu et al., JASN 14: 2305-2312, 2003

- ☆ Post-hoc analysis of the MDRD study, comparing *early* (predicted MDRD GFR > 7.5 ml/min ; *N= 1444*) with *late* (predicted GFR <7.5 ml/min; *N= 1476*).
- ☆ Higher MDRD GFR at initiation was associated with ***an increased risk of death*** in multivariate Cox model (hazard ratio 1.27 for each 5 ml/min increase).
- ✓ Reflect an erroneous estimation by MDRD formula

Conclusion: the data do not support early initiation of dialysis.

Who (has) said early dialysis is bad

Kazmi et al., Am J Kidney Dis. 2005 Nov; 46(5): 887-96

- ☆ Undertook an evaluation of the impact of comorbidity on the association between GFR at initiation and death results: greater GFR at initiation associated with **a greater risk for death** in all population.
- ☆ Patients in the general dialysis population who initiated dialysis therapy at a GFR > 10 ml/min/ 1.73 m² had a **42% increased risk for death** compared with patients with a GFR < 5 ml/min/ 1.73 m² At initiation of dialysis after adjusting for all covariates.
- ✓ **Recommendation:** Additional research required

Who (has) said early dialysis is bad

Wilson et al., Hemodial Int **2007** (Canada)

- ✓ Retrospective cross-sectional study **n = 271**
- ✓ **17%** started haemodialysis late (GFR<5), These patients ...
 - Were younger (p=0.008)
 - More females (p=0.013)
 - More employed (p=0.051)
 - Less cardiac disease (p<0.001)
 - Less peripheral vascular disease (p=0.031)
 - Lower serum albumin (p=0.023)
- ✓ At year 1 = no difference in mortality
- ✓ At year 2 = the earlier the dialysis start, the greater the mortality rate (p=0.022).

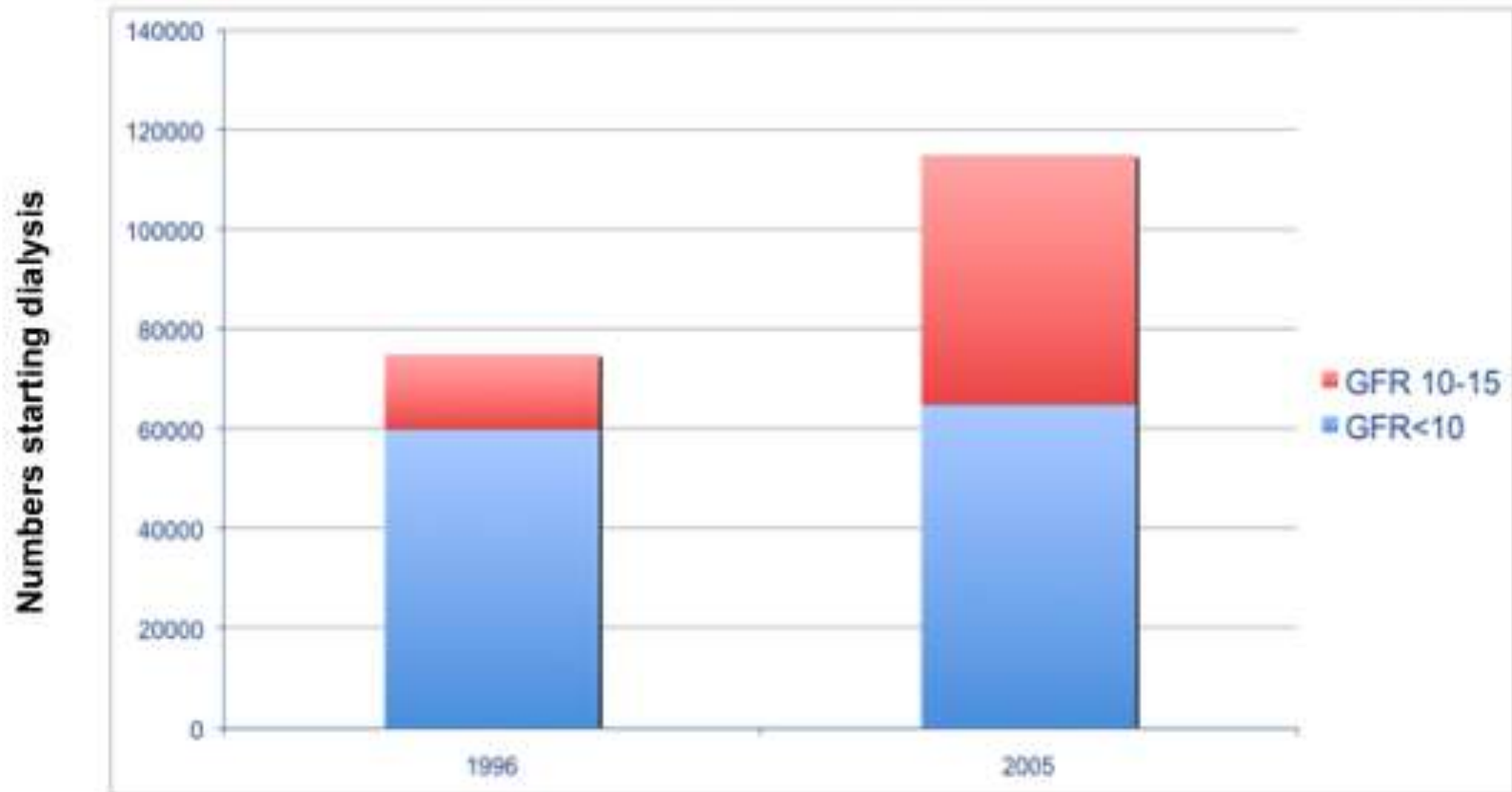
Who (has) said early dialysis is bad

Wright et al., CJASN 2010 (USA)

- ✓ Retrospective USRDS analysis ... **n = 896,546** with Cox model adjusting for potential confounding variables.
- ✓ **The reference group** had an eGFR of >5.1 to 10
- ✓ **99,231 (11%)** had an early start (eGFR >15). This 11% were ...
 - More white
 - More male
 - Had higher co-morbidity with more diabetes
 - More selected peritoneal dialysis
- ✓ **113,510 (12%)** had a late start (eGFR ≤5)
- ✓ Early start group had an increased risk of mortality
- ✓ Late start group had a reduced risk of mortality

CONCLUSION: Late start is associated with better survival

Who (has) said early dialysis is bad



Who (has) said early dialysis is bad

Rosansky et al., 2011 USA:

- ✓ 81,176. non-diabetic, 20-64 years in-center incident HD patients.
- ✓ No co-morbidities other than hypertension .

- ✓ Unadjusted 1-year mortality by eGFR ranged from:
 - 6.8% in the reference group (e GFR <5.0 ml/min)

Ranges to

- 21.1% in the highest e GFR group (eGFR \geq 15 ml/min)

- ✓ The HR for one year mortality was:

- eGFR <5.0 ml/min = 1
- eGFR 5-9.9 ml/min = 1.27
- eGFR 10-14.9 ml/min = 1.53
- eGFR \geq 15 ml/min = 2.18

Who (has) said early dialysis is bad

Evans et al., J Intern Med **2011** (Sweden)

- ✓ Population-based, prospective, observational cohort study ... **n = 901**
- ✓ Early-start dialysis
eGFR ≥ 7.5 = 52% died
- ✓ Late start dialysis
eGFR < 7.5 = 36% died
- ✓ The adjusted HR for death was 0.84 (95% CI = 0.64, 1.10) for late start
- ✓ No dialysis ... mortality started to increase significantly at eGFR < 7.5

Conclusion: No survival benefit from early initiation of dialysis

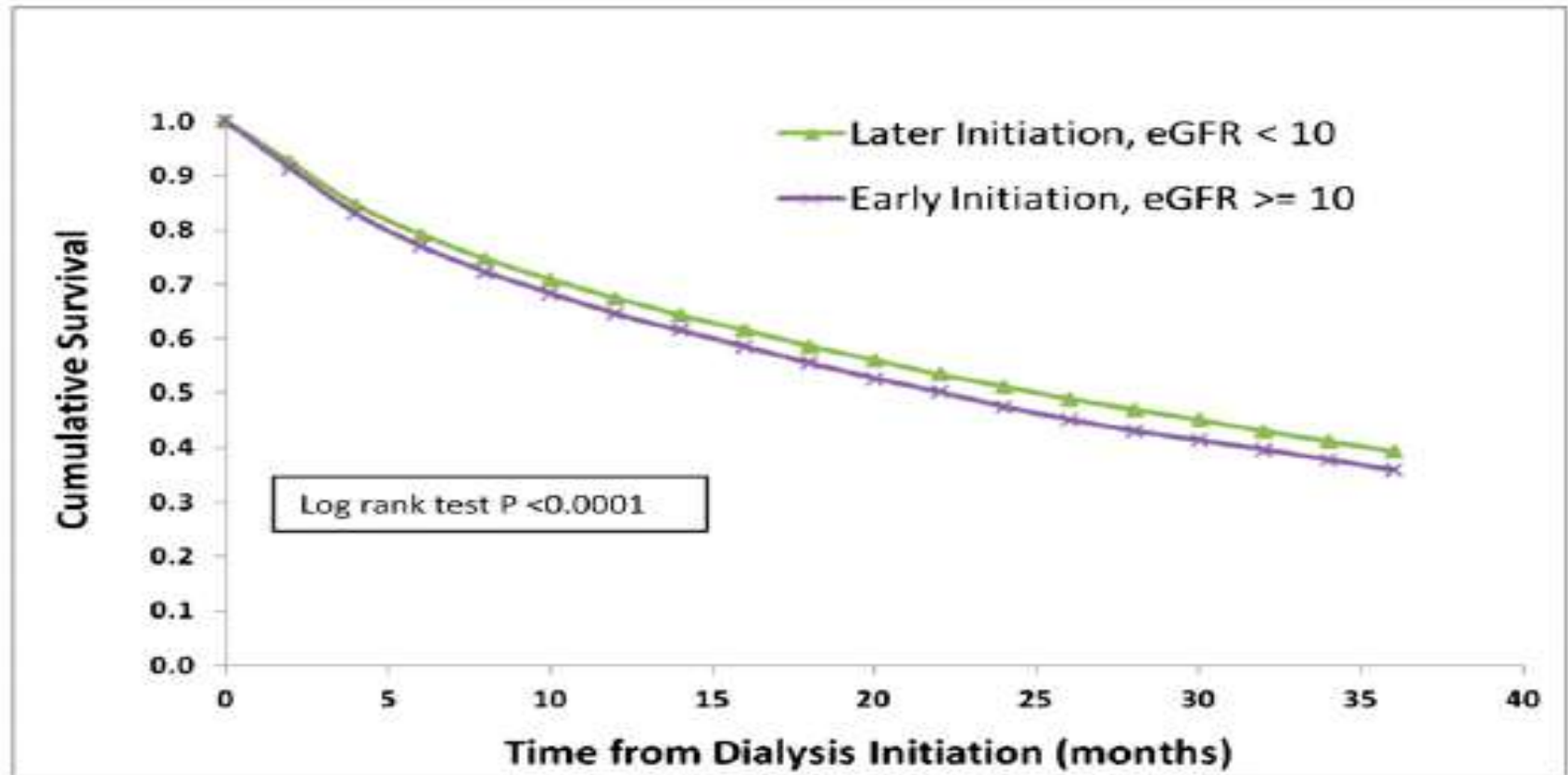


Figure 2. Proportion of patients surviving from time of dialysis initiation, among those initiating at eGFR <10 and ≥ 10 ml/min per 1.73 m^2 .



Is the problem really
‘late start’

or is it just
‘late referral’

Nephrological Referral

- ✓ Early nephrological referral and predialysis care are essentials to prolong patient's survival.
- ✓ Studies suggest increased all-cause mortality in patients referred late.
- ✓ It often occurs **late** Due to both patient and physician **biases**.

Why so early?

- ✓ CKD can progress at different rates.
- ✓ Reversible causes (vasculitis, etc).
- ✓ Management of comorbidities (Anemia, bone-mineral metabolism, hypertension, malnutrition).
- ✓ Discussion of dialysis modalities and transplantation.
- ✓ Early creation of dialysis access.
- ✓ Decrease need for urgent dialysis.



Late Nephrological Referral

Kazami et al., NDT 2004:

Late nephrology referral and mortality among patients with end stage renal disease: a propensity score analysis.

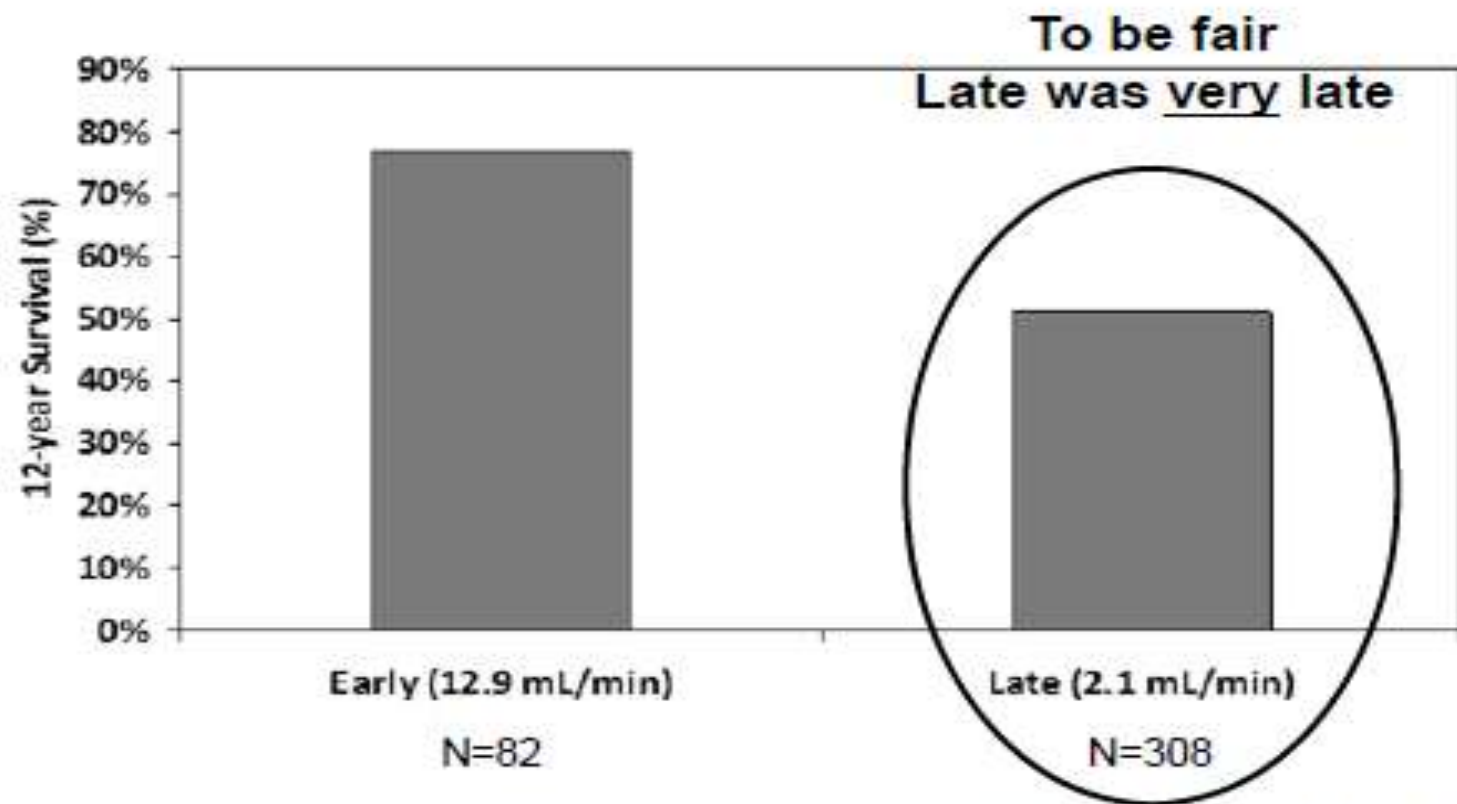
- Dialysis Morbidity and Mortality Study = a prospective study of incident dialysis patients.
- Late referral = first nephrology visit <4 months.
- Propensity scores were estimated for **2195** patients.
- 54% were males, 66% were Caucasians, 26% were African-American.
- 33% were referred late.
- Late referral carried a 44% higher risk of death at 1 year.



CONCLUSION:

Late referral was associated with higher risk of death at 1 year after initiation of dialysis compared with early referral.

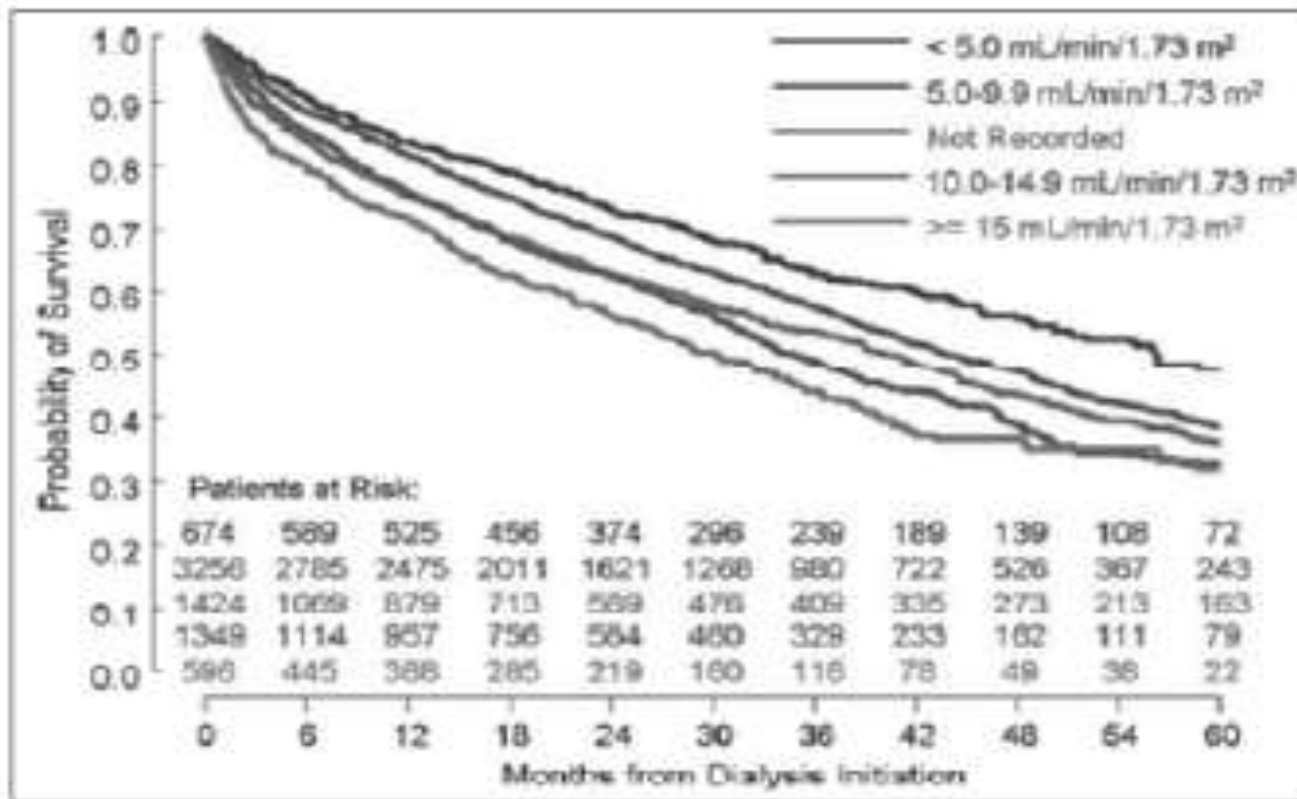
1978: The origin of 'early start' dialysis



Bonomini et al Kidney Int 13:S112-8, 1978

Evidence (2009)

European Registry data(ERD) showed that patients who start early do worse when compared with those who start late!



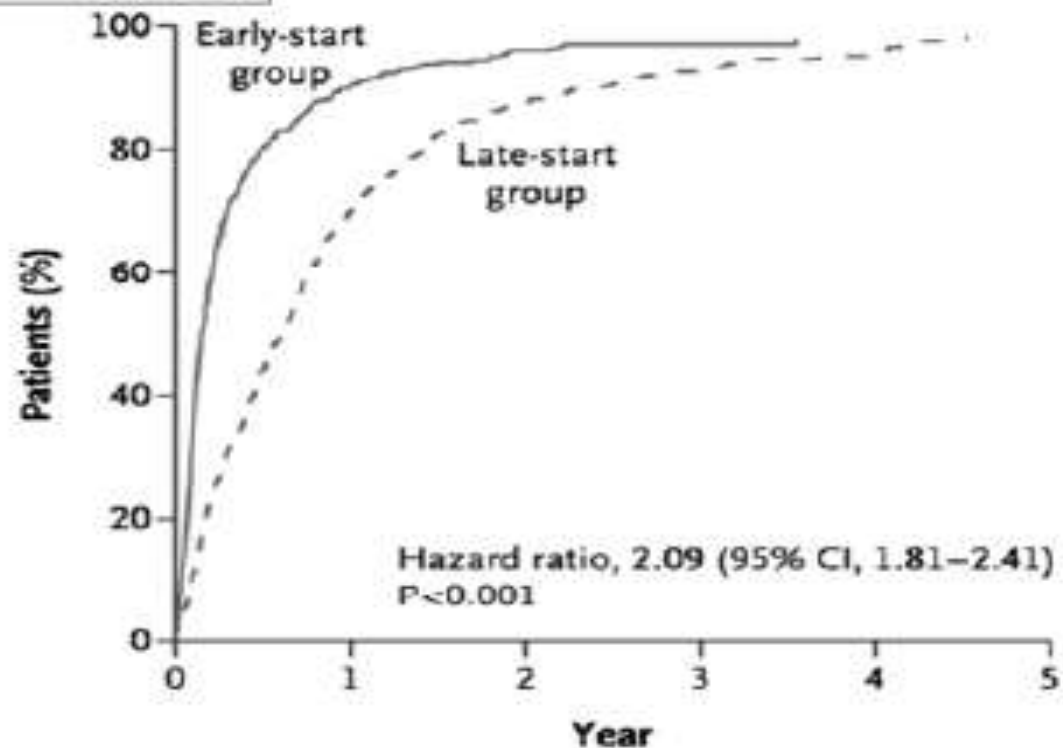
Evidence (2009)..... and bias

While ...

- ✓ Registry data shows patients starting early do worse ...
- ✓ **Biases** exist with these type of reviews as ...
 - Sicker patients will commonly be started early
 - Well patients with less co-morbidity will start later

Problem ... no RCT!

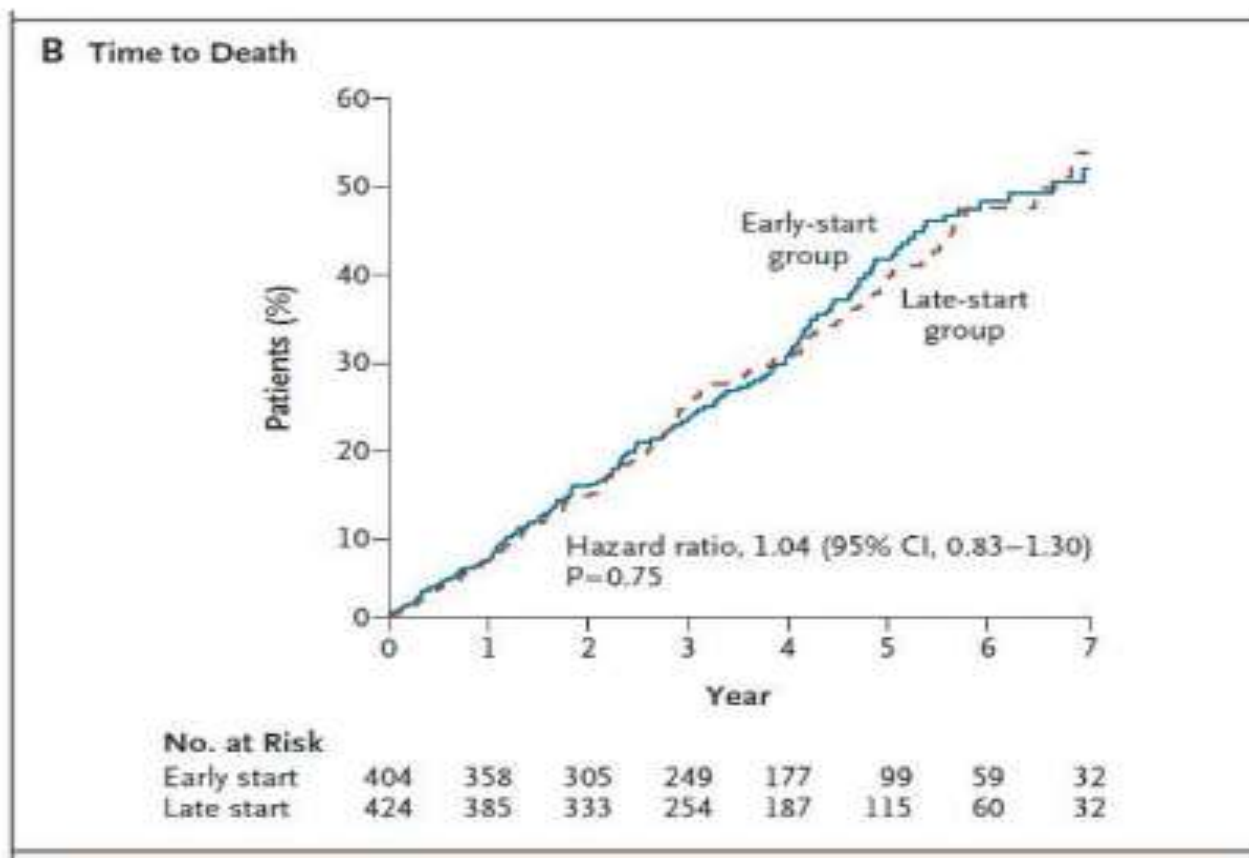
Time to starting dialysis



Good separation

No. at Risk

Early start	404	35	12	8	2	1
Late start	424	118	45	21	9	3



N Engl J Med 2010;363:609-19.

A better way to use eGFR in CKD5

✓ *eGFR should NOT be the lone trigger for dialysis*

But ...

✓ *eGFR is an IDEAL 'trigger' to script its' preparation*

✓ In-build automated eGFR prompts in your EMR to:

- | | |
|------------|---|
| eGFR 20-22 | * Trigger education program referral |
| eGFR 20 | * Trigger MSW review of services and supports |
| eGFR 18-20 | * Trigger vein map + multidisciplinary AVF clinic |
| eGFR 13-15 | * Trigger 2nd stage AVF surgery + home review |
| eGFR 12 | * Trigger final check list that all is done and working |
| | * Trigger closer review for pre-CKD5d symptoms |

Conclusions

- ✓ It can be reasonably stated that timely initiation of dialysis treatment cannot be based merely on numerical data, but should be decided according to the overall clinical tolerance of each individual patient according to his or her advanced stage of uremia.
- ✓ Early dialysis initiation are not upheld by facts and evidence, and that early dialysis initiation does not consistently provide a mortality, morbidity, or quality of life benefit, unless accompanied by compelling reasons for initiating treatment.
- ✓ Early dialysis initiation using creatinine-based eGFR for decision making may be harmful.

Conclusions

- ✓ Survival is not diminished by late start – only by late referral. Late referral the enemy, not the eGFR alone.
- ✓ Initiating dialysis at the right time for a given patient with the most appropriate technique represent a sophisticated exercise of clinical medicine, which remains, and will remain a balanced mixture of science and art.
- ✓ Future studies examining indications for dialysis initiation and outcomes will contribute to evidence-based guidelines concerning the optimal timing for dialysis initiation.

Thank You

